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14. ABSTRACT
The major hypothesis is that prior occupational exposure to polychlorinated biphenyls (PCBs) results in decrements in neuropsychological and neurological performance and that these deficits are related to reductions in the number of dopamine (DA) terminals in the basal ganglia. In Albany, NY 248 former capacitor workers (62 per year) will undergo neuropsychological and neurological examinations, complete a comprehensive questionnaire, have blood drawn to measure serum thyroid hormone and PCB concentrations, and undergo a non-invasive test to determine bone-lead concentrations. This latter measure will allow us to control for exposure to lead--a potential confounder. In New Haven, CT 96 subjects (24 subjects per year) will be asked to undergo brain imaging at the Institute for Neurodegenerative Disorders to determine if PCBs reduce the number of basal ganglia DA terminals. To date, 217 subjects have undergone testing in Albany and 73 have been imaged in New Haven, CT with additional subjects scheduled for testing. Serum PCB concentrations are being analyzed at Mt. Sinai School of Medicine. Secure electronic databases have been created for all data.

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Polychlorinated Biphenyls, Dopamine, Parkinson's Disease, Neurological Function, Aging

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INTRODUCTION

The major hypotheses to be tested in this project are that high-level occupational exposure of former capacitor workers to polychlorinated biphenyls (PCBs) will result in reductions in (i) performance on neuropsychological and neurological tests that reflect the historic PCB body burden of the individual; (ii) the number of dopamine (DA) terminals in the basal ganglia that correlate with behavioral change and (iii) circulating levels of thyroid hormones.

Aging former capacitor workers, previously employed at capacitor manufacturing facilities located approximately fifty miles north of Albany, NY, are undergoing neuropsychological and neurological exams, completing a comprehensive occupational, residential and dietary questionnaire, having blood drawn to measure serum thyroid hormone and PCB concentrations, and undergoing a non-invasive test to determine bone lead concentrations in Albany, NY. This latter measure will reduce the likelihood of confounding the neurological effects of prior PCB exposure with the neurological effects of prior lead exposure. Finally, approximately 40% of the subjects are also participating in a second portion of the study that uses brain β-CIT SPECT imaging to determine whether prior occupational exposure to PCBs reduces the number of basal ganglia DA terminals. Imaging takes place at the Institute for Neurodegenerative Disorders in New Haven, CT under the supervision of Dr. Kenneth Marek.

In order to test the above hypotheses we have gathered a team of internationally recognized experts in the epidemiology of environmental and occupational exposure to PCBs, the neurology of movement disorders and Parkinson's Disease, the assessment of toxicant-induced deficits in neuropsychological function, measurement of serum PCB concentrations, non-invasive determination of bone lead concentrations, and brain imaging of central DA neurons and their relationship to movement disorders, including Parkinson's Disease. As described more fully on the following pages, we have made considerable progress in reaching our goal of testing 248 former capacitor workers.

STUDY INVESTIGATORS

Albany, NY Based Testing

Richard F. Seegal - Wadsworth Center, New York Sate Dept. of Health (NYSDOH): Principal Investigator

Edward F. Fitzgerald – University at Albany, School of Public Health and
Lenore J. Gensburg - Center for Environmental Health, NYSDOH: Tracing, Screening, Residential, Occupational, Dietary and Medical Histories

Eric S. Molho, Donald S. Higgins - Albany Medical Center: Neurological Assessment

Stewart A. Factor - Emory University: Neurology Consultant

Robert J. McCaffrey - University at Albany: Neuropsychological Assessment

Richard F. Haase - University at Albany: Biostatistician

Mary S. Wolff - Mount Sinai School of Medicine: Serum PCB Analyses

Andrew S. Todd - Mount Sinai School of Medicine: Bone Lead Determination

Patrick Parsons - Wadsworth Center, NYSDOH: Bone Lead Determination

New Haven, CT Based Testing

Kenneth Marek, John P. Seibyl, Danna Jennings - Institute for Neurodegenerative Disorders: ß-CIT SPECT Brain Imaging

What Has Changed This Year?

Personnel

Ms. Lakhana Weaver who was hired (50% effort) to carry out the bone lead measurements has left employment. Her duties are being shared by other staff for the remaining several months of data collection.

We Are Collecting Sera for Analysis of Thyroid Hormone Function

We received IRB approval in early 2004 and began collecting in May 2004 an additional tube of blood from each subject (one tube is for analysis of serum PCB concentrations) in order to determine thyroid hormone function (T_3, 3,5,3-Triidothyronine; T_4, Thyroxine; Free T_3; Free T_4; and TSH, Thyroid Stimulating Hormone levels). We have presently collected an additional blood sample from 137 subjects. In March of 2005 we requested modification of the Statement of Work (SOW) and $16,000 in additional monies to carry out the above described analyses. This request was approved on August 3, 2005.

We Have Modified Our Procedures for Selecting Subjects for Inclusion in the Study

We initially randomly selected subjects from computer lists that contain the names and addresses of all individuals who worked for at least three months at either the Ft. Edward or Hudson Falls, NY capacitor plants. However, examination of job description codes for prospective subjects who had not participated in the earlier study by scientists from Mt. Sinai Medical Center (*i.e.,* those with archived sera) demonstrated that approximately $1/3^{rd}$ of the subjects did not have any jobs that involved exposure to PCBs. In order to increase the number of subjects drawn from the population of exposed workers we have increased subject recruitment from those individuals whose job codes indicate past exposure to PCBs. To adjust for the resulting oversampling of male subjects, we have subsequently increased our sampling of female subjects. This change will result in our test sample more closely approximating the gender composition of the full cohort of 6798 capacitor factory worker. As a consequence of this decision, we will be able to more adequately examine for potential gender differences in the dependent variables that we are testing.

Progress in Fiscal Year 2004

The following narrative provides descriptions of the progress we have made in the fourth year of the project (third year of data collection)—a period in which we have been actively engaged in data collection.

We Have Reached Our Goal for Recruiting and Testing Subjects in 2005

In the past year we successfully recruited and tested 89 subjects in Albany, NY. As of 31 December 2005 we have tested a total of 217 subjects, with seven additional subjects still scheduled (see Table I), and are thus on schedule toward completing testing of 248 subjects. See also Appendix 1 for a summary of the demographics for the tracing and screening activity to date. The tests conducted in Albany include: (i) administering a residential, occupational, dietary and medical history interview; (ii) completing neurological and neuropsychological assessments; (iii) measuring bone lead concentrations and (iv) collecting blood for measurement of serum thyroid hormone and PCB concentrations.

TABLE I: Albany, NY Testing, Potential Subjects as of 31 Dec '05
n=444 (10 still in recruitment)

	YES: 224 217 Complete and 7 Scheduled		NO: 210	
GENDER				
Male	128	57.14%	103	49.05%
Female	96	42.86%	107	50.95%
AGE				
50s	85	37.95%	75	35.71%
60s	70	31.25%	52	24.76%
70s	57	25.45%	57	27.14%
80-90s	12	5.36%	26	12.38%

At completion of testing in Albany, subjects were asked if they wished to participate in the SPECT β-CIT imaging portion of the study carried out by Dr. Marek's group at the Institute for Neurodegenerative Disorders in New Haven, CT. Despite the fact that these procedures require a two day stay in New Haven and the injection of a radio-labeled tracer, we have met our goal of testing 24 subjects per year. These data are presented in Table II.

TABLE II: New Haven, CT Testing, Potential Subjects as of 31 Dec '05
Subjects n=217 (23 still in recruitment)

	YES: 78 73 Complete and 5 Scheduled		NO: 116	
GENDER				
Male	50	64.10%	71	61.21%
Female	28	35.90%	45	38.79%
AGE				
50s	29	37.18%	42	36.21%
60s	34	43.59%	28	24.14%
70s	13	16.67%	38	32.76%
80-90s	2	2.56%	8	6.90%

Table III provides a summary of tracing, screening and recruitment for individuals selected from the cohort through 31 December 2005. Tracing refers to the procedures carried out to identify and locate individuals who potentially could take part in the study, while screening refers to the procedures carried out by staff at the Center for Environmental Health (a part of the New York State Department of Health) to determine if the individuals are medically eligible. If found eligible, the subjects' names were sent to the Study Coordinator, who contacted them to more completely describe the test protocols and schedule their visits to Albany.

TABLE III: Subjects Selected from Cohort (n=6798) as of 31 Dec '05

Tracing Results	**Entered Tracing: 2670**	
Dead	801	30.00%
Out of Area	230	8.61%
Too Young	0	0.00%
Could not be Located	433	16.22%
Eligible for Screening	**1071**	**40.11%**
Still in Tracing	135	5.06%

Screening Results	**Entered Screening: 1071**	
Refused	190	17.74%
Ineligible-Medical	300	28.01%
Ineligible-Non-Medical	51	4.76%
Eligible for Recruitment	**444**	**41.46%**
Still in Screening	86	8.03%

Albany Testing: Recruitment Results	**Entered Recruitment: 444**	
Participated + Scheduled (7)	**244**	**50.45%**
Refused	210	47.30%
Still in Recruitment	10	2.25%

New Haven Testing: Recruitment Results	**Entered Recruitment: 224**	
Participated + Scheduled (5)	**78**	**34.82%**
Refused	116	51.79%
Still in Recruitment	30	13.39%

Table IV provides a summary of subject participation in the Albany, NY and New Haven, CT portions of study from inception through 31 December 2005.

TABLE IV: Summary of Subject Participation as of 31 Dec '05

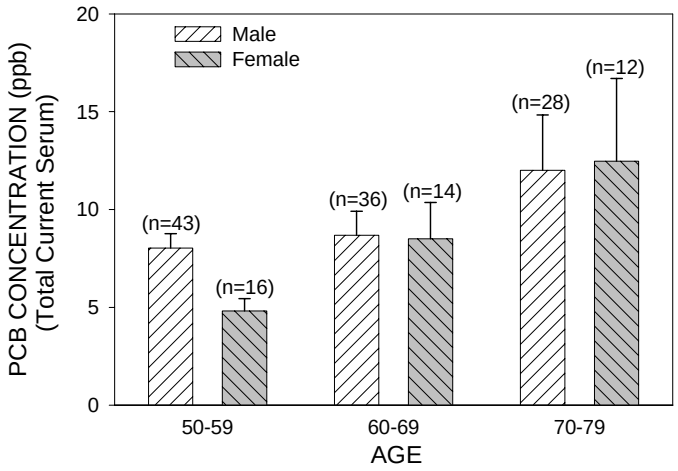
	All Subjects	
Albany Participation		
Yes, Participated	217	49%
Yes, Scheduled	7	2%
To Be Contacted/Recruit Later	10	2%
Refused	210	47%
TOTAL	**444**	**100%**
New Haven Participation		
Yes, Participated	73	34%
Yes, Scheduled	5	2%
To Be Contacted/Recruit Later	11	5%
Not Contacted	12	6%
Refused	116	53%
TOTAL	**217**	**100%**

Measurement of Serum PCB Concentrations

Dr. Mary Wolf, of the Mt. Sinai School of Medicine, is analyzing serum PCB concentrations from the former capacitor workers using glass capillary gas chromatographic techniques. Data includes not only congener specific determination of current serum PCB concentrations, obtained when the subjects travel to Albany, but also, for those individuals for whom we have archived sera, re-analysis using the same analytical procedures described in the grant application. The availability of both current and archived sera PCB levels, determined in the same laboratory using the same analytical techniques, allows us to more precisely estimate historic serum PCB levels for those individuals for whom we do not have archived sera.

The data presented below represents PCB analyses from the first 157 subjects broken down by age (decade) and gender (data for the decade 80-89 is not presented because of the small N). It is noteworthy that the serum PCB levels remain elevated (average PCB levels in non-occupationally-exposed individuals are approximately 2-3 ppb) more than twenty-five years after occupational exposure ceased. Although we chose to present only total PCB concentrations (a sum of lightly and heavily chlorinated congeners), subsequent analyses, particularly for levels of lightly chlorinated congeners that have short half-lives, will allow us to discriminate between occupational and more recent recreational and/or residential exposures.

Figure 1. Total Current Serum PCB Levels (mean ± sem)



Measurement of Bone Lead Concentrations by K-Shell X-Ray Fluoresence

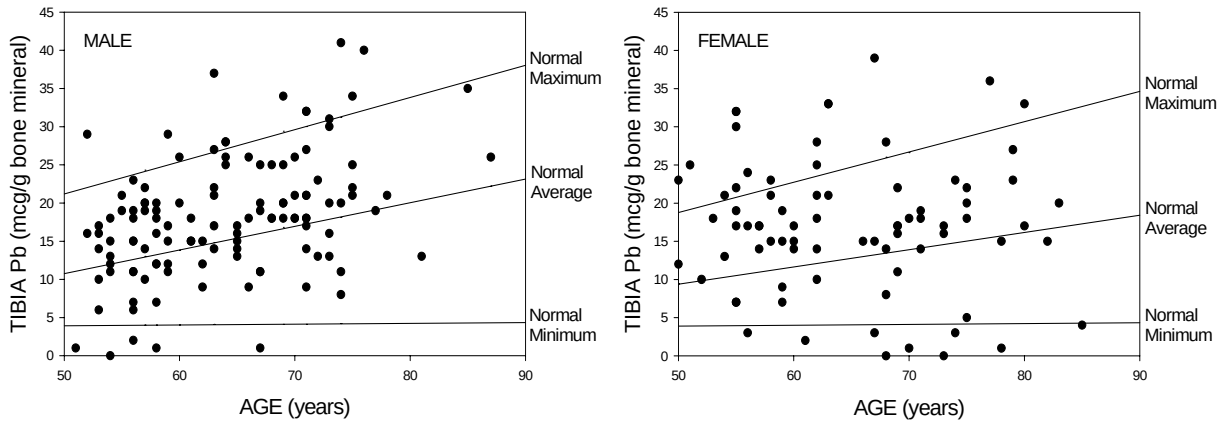
Mount Sinai supervised the *in vivo* measurement of lead in bone in Albany and analyzed the raw data (in electronic form) generated with the bone lead measurement system. Mount Sinai personnel also continued to provide consultation on all aspects of the X-ray Fluorescence bone lead measurement system, including regular and *ad hoc* consultation, as required, on the quality of spectra acquired, the control and use of the measurement system and the reliability of the analytical results in order to provide both the most precise and the most reliable bone-lead data possible.

Mount Sinai personnel also supervised the Albany XRF operators in the daily operation of the XRF measurement system with regard to its maintenance, calibration, optimization and quality control protocol and have provided expertise on the optimization of the measurement system with regard to operational parameters of the spectroscopy electronics (*viz.* rise time, flat-top, *etc.*).

All calibration and human measurement XRF data have been electronically transmitted to the Mount Sinai XRF Laboratory for analysis. The analyses of the data received to date have been completed. Analyses of new data are being performed as they arrive. To date, sixty study participants have had their bone lead measured and analyzed. These bone lead data for the first 204 subjects are presented below.

The range of values for ‘maximum’ and ‘minimum’ are based on data from 13-16 studies of XRF measurement of bone lead concentrations obtained from non-occupationally-exposed men and women (Roy *et al., Appl. Radiat. Isotopes*, 48, 391-6, 1997; Gamblin *et al., Appl. Radiat. Isotopes*, 45, 1035-8, 1994) and are presented here to provide a framework in which to begin to interpret the concentrations of bone lead we have determined in the former capacitor workers.

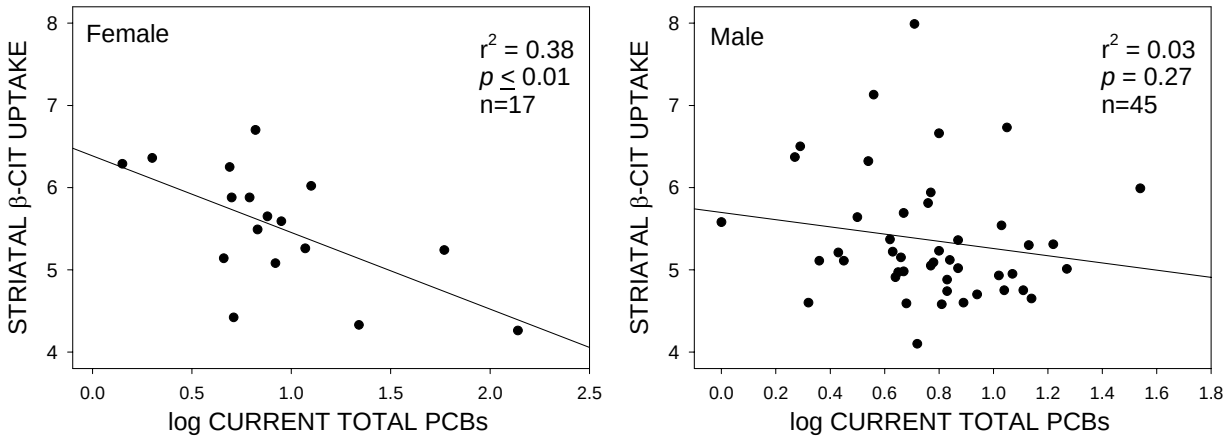
Figure 2. Tibia Lead (Pb) Concentrations by Age and Gender



Measurement of Brain Dopamine Transporter by β-CIT SPECT Imaging

Preliminary analysis of the data yielded a significant statistical relationship between dopamine transporter density measured by β-CIT SPECT imaging and current serum total PCB concentrations which was observed only in female former capacitor workers. This measurement represents the average uptake of the radio-labeled ligand [^{123}I]β-CIT in the putamen and caudate of male and female former exposed workers measured by SPECT imaging, providing an *in*-vivo measure of dopamine transporter density. Total PCB levels were measured in serum from the subjects at the time of imaging. The significant negative relationship seen only in female workers—all who were postmenopausal—has allowed us to formulate a hypothesis that estrogen withdrawal increases risk of basal ganglia dopamine dysfunction only in women (see also Conclusion).

Figure 3. Dopamine Terminal Density Measured by β-CIT SPECT Imaging as a Function of Current Serum PCB Concentrations



Measurement of Serum Thyroid Hormone Function

Analysis of serum samples collected for thyroid hormone function (T_3, T_4, free T_3, free T_4, and TSH levels) is being conducted by the clinical chemistry group of the Clinical Laboratory Evaluation Program of the New York Sate Department of Health. The first 85, out of an anticipated 160 serum samples, to be collected for thyroid hormone function have been analyzed to date. These data, summarized by gender, are presented in Table V. Preliminary examination of the data indicates that most of the data falls within the normal ranges for these measures.

TABLE V: Thyroid Hormone Level in Serum

	Male (N=66)		Female (N=19)	
Thyroid Hormone Measure	**Mean**	**s.d.**	**Mean**	**s.d.**
TSH	2.07	1.13	2.22	1.34
T4	8.00	1.54	9.24	1.63
Free T4	1.23	0.16	1.30	0.19
T3	133.05	26.36	126.25	23.02
FreeT3	5.32	0.72	4.82	0.67

THS = Thyroid Stimulating Hormone
T4 = Thyroxine
T3 = 3,5,3-Triidothyronine

Investigators Meetings and Communication with Participants

In order to facilitate communication between researchers who are located at the different institutions in Albany, we have met quarterly during the past year (March 16th, June 30th, September 20th and December 15th). These meetings have proven to be extremely useful and allow us to avoid many of the pitfalls that might otherwise occur in the conduct of this complicated multi-institutional epidemiological study. Topics discussed included modifications to phone screening to include chemotherapy and radiation questions, revisions to reproductive section of the interview form to include definitive age at menopause and hormone replacement therapy questions as well as subject selection.

With the end of data collection to take place by approximately May 2006, we have scheduled the next annual meeting of all investigators and staff to be held in Albany in June of this year to discuss data analysis and the reporting of results.

In Appendix 2 we include a copy of the most recent study update that was sent to all study participants. We feel strongly that communication with participants is an important component of maintaining goodwill in the community.

KEY RESEARCH ACCOMPLISHMENTS

As in all epidemiological studies, presentation of interim results prior to the collection of the entire data set and the accompanying statistical analyses to control for potential confounders is at best misleading and at worse may result in conclusions that are fallacious. Hence, the key research accomplishments are those described in the above sections.

REPORTABLE OUTCOMES

Two abstracts that included data from this study were presented during the past year at scientific conferences. The first, entitled 'Biological Bases for PCB Induced Alterations in Dopamine-Mediated Neurological Function' was presented in March 2005 at the Annual meeting of the Society of Toxicology in New Orleans, LA. In September 2005, I presented a talk entitled 'Polychlorinated Biphenyls Alter Dopamine Function in Older Capacitor Workers' at the invitation of the U.S. Army in a session jointly sponsored by the U.S. Army Research Institute of Environmental Medicine and the U.S. Army Medical Research and Materiel Command entitled 'Neurotoxicant Exposure in Military Deployments and Putative Associations with Neurodegenerative Diseases' at the Twenty-Second International Neurotoxicology Conference in Research Triangle Park, NC (see Appendix 3).

In addition, in April 2005 I presented a lecture entitled 'PCB Exposure and Parkinson's Disease' in the Toxic Risks with Aging–2005 Spring Symposium at Duke University sponsored by the Duke University Integrated Toxicology Program, Superfund Basic Research Program, Center for the Study of Aging and Human Development, and the National Institute of Environmental Health Science.

CONCLUSIONS

For the third year we have met our goal for recruiting and testing subjects, both in Albany, NY and in New Haven, CT. We are proud of this progress since many of our subjects are elderly and must travel considerable distances to undergo testing at these two sites.

We are nearing the end of the data collection portion of the study (as of 31 December 2005 we have tested 217 subjects out of our goal of 248 subjects) and can now begin to carefully review the data to determine initial trends. For example, interim data analyses have demonstrated a highly significant negative correlation between current PCB serum concentrations and β-CIT SPECT imaging of dopamine transporter density in the caudate/putamen that is only seen in women. Based on these preliminary results extra, effort is being made to adequately represent women among our study participants and we will continue to do so for the remaining tenure of the grant. This unexpected finding is supported by a recent publication by Steenland *et al.* (*Epidemiology* **17**(1), 8-13, 2006) that demonstrated increased Parkinson's disease mortality only in female former capacitor workers.

We continue to show that current serum PCB levels are significantly elevated in former capacitor workers compared to literature values for non-occupationally exposed individuals. These findings demonstrate, given the many years since occupational exposure ceased, the extraordinarily high levels of PCBs to which these workers had been exposed.

Finally, we are analyzing sera to determine whether occupational exposure has altered thyroid hormone function in these workers. We will use that information to statistically determine the contributions of endocrine disruption, in addition to those hypothesized to occur following reductions in central dopamine function on neurological, neurobehavioral and imaging outcomes.

APPENDICES

Appendix 1: Demographic Outcomes for Tracing and Screening Activity to Date.

Appendix 2: Recent Study Update for Participants.

Appendix 3: Abstracts from Society of Toxicology, New Orleans, LA, March 2005 and International Neurotoxicology Conference, Research Triangle Park, NC, September 2005.

APPENDIX 1

Demographic Outcomes for Tracing and Screening Activity to Date

Capacitor Workers Study

Traced to Date: 2770

DEMOGRAPHICS: OVERVIEW

	n	%
Sex		
Female	1532	55.31%
Male	1238	44.69%
Agegroup		
50s	618	22.31%
60s	542	19.57%
70s	705	25.45%
80s+	903	32.60%
Unknown	2	0.07%

DEMOGRAPHICS: BY TRACING OUTCOME

Sex	Eligible for Screening (n=1109)	
Female	598	53.92%
Male	511	46.08%
	Not Eligible for Screening (n=1493)	
Female	766	51.31%
Male	727	48.69%
Agegroup	Eligible for Screening (n=1109)	
50s	376	33.90%
60s	287	25.88%
70s	297	26.78%
80s+	149	13.44%
	Not Eligible for Screening (n=1493)	
50s	224	15.00%
60s	213	14.27%
70s	366	24.51%
80s+	688	46.08%
Unknown	2	0.13%

Capacitor Workers Study

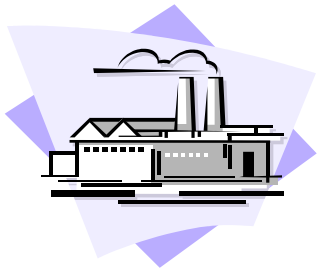
Traced to Date: 2770

DEMOGRAPHICS: BY SCREENING OUTCOME

Sex	Refused (n=195)	
Female	114	58.46%
Male	81	41.54%
	Medically Ineligible (n=306)	
Female	172	56.21%
Male	134	43.79%
	Non-Medically Ineligible (n=54)	
Female	36	66.67%
Male	18	33.33%
	Passed to Recruitment (n=455)	
Female	222	48.79%
Male	233	51.21%
Agegroup	Refused (n=195)	
50s	59	30.26%
60s	45	23.08%
70s	54	27.69%
80s+	37	18.97%
	Medically Ineligible (n=306)	
50s	97	31.70%
60s	85	27.78%
70s	93	30.39%
80s+	31	10.13%
	Non-Medically Ineligible (n=54)	
50s	5	9.26%
60s	6	11.11%
70s	11	20.37%
80s+	32	59.26%
	Passed to Recruitment (n=455)	
50s	169	37.14%
60s	128	28.13%
70s	118	25.93%
80s+	40	8.79%

APPENDIX 2

Recent Study Update for Participants



The Capacitor Workers Study

Status Report – Winter 2006

Rich's Corner

Why Test Thyroid Function?

PCBs were developed for industrial use as compared to drugs which are designed for a specific purpose and have a known mechanism of action. PCBs cause many biological changes. They can alter hormonal function in addition to directly affecting brain function. Indeed, in studies of both laboratory animals and humans, PCBs reduced blood levels of thyroid hormones.

Low levels of thyroid hormones, a condition known as hypothyroidism, may be associated with decreases in brain function, learning and behavior. We added the measurement of blood thyroid hormone levels to our study to help us better understand how occupational exposure to PCBs affects brain function and behavior. Please feel free to contact me toll-free at 1-866-852-2561 if you have any questions about the study.

Project Background

Dr. Rich Seegal received funds in 2002 to carry out a study of the long-range neurological health risks associated with occupational exposure to polychlorinated biphenyls (PCBs). This epidemiological study is funded by the United States Army Medical Research and Materiel Command. Professionals from the following institutions are collaborating on the study: New York State Department of Health, Albany Medical Center, University at Albany, Mt. Sinai School of Medicine, Institute for Neurodegenerative Studies in New Haven, CT.

We hope to evaluate 250 former capacitor workers who, like you, were employed by the General Electric capacitor factories in either Fort Edward or Hudson Falls. This study differs significantly from earlier ones because of our emphasis on the effects of PCBs on brain function and behavior.

Why study PCBS?

Based on studies of pregnant women who consumed PCB-contaminated fish, PCB exposure has been associated with lower scores on measures of memory and learning in their infants and children. Similarly, recent studies suggest that consumption of PCB-contaminated sport-caught fish by adults may also lead to poorer scores on tests of learning. Nevertheless, the effects of PCBs on the adult nervous system remain poorly understood.

One reason for this lack of understanding may be that studies of fish consumption have incorrectly assumed that PCBs are solely responsible for the observed changes. Fish--particularly fish from the Great Lakes--contain a number of other chemicals that may contribute to the deficits in brain function. Still, while capacitor workers may have been exposed on the job to other substances that affect brain function, such as lead, the major exposure was to PCBs.

Status Update

Participants in the Albany-based portion of the study began their testing in January 2003. Medically eligible former capacitor workers who lived within 100 miles of the Capital District came to Albany for an interview, a blood test to measure current PCB levels, non-invasive testing of the nervous system, and an x-ray of the shin bone to determine past exposure to lead. An additional blood test used to determine thyroid function was added to the research protocol in May 2004.

As of December 31, 2005, two hundred and seventeen men and women have participated in the project. The participants have ranged in age from 50 to 87 years! We have added an

additional day of testing and now offer appointments on Monday, Wednesday and Friday. We are hoping to achieve a study sample size of 250 by this spring.

We appreciate your participation!

In a large-scale study of this kind, known as an epidemiological study, one of the most important factors in evaluating the overall success of the project is the rate of participation. So far, almost 50 percent of workers asked to participate have agreed to do so. We are extremely appreciative of your response and support of this research study.

How can this information be of use?

Understanding the relationships between previous occupational exposure to PCBs and possible changes in nervous system function may ultimately lead to better treatment of workers who have been exposed to high levels of PCBs. This information may also help us understand the role of brominated fire retardants in our environment. These chemicals may have similar toxic effects as PCBs and are now found at fairly high levels in both the environment and in humans.

The Connecticut study update

One mechanism by which PCBs may alter brain function is by decreasing concentrations of a brain chemical called dopamine. Indeed, studies of laboratory animals show that PCBs cause a reduction in the amount of dopamine in the brain.

We began the Connecticut-based study in April 2003. This second part of the study provides additional information on the effects of PCBs on the brain through the use of a brain imaging technology known as SPECT. This imaging allows physicians to actually measure the number of dopamine-containing brain cells that a person has. The Connecticut portion of the study will help us understand **how** PCBs alter brain function by determining if exposure to PCBs on the job reduces the number of brain cells that contain dopamine.

All of the people who complete the testing in Albany are invited to participate in the Connecticut part of our study. As with the Albany study, the rate of participation in the Connecticut study has been exceptional. Seventy three people have traveled to Connecticut and completed the testing there. Past participants have made the following comments about their experience:

"The trip to New Haven went without a hitch."

"The people, facilities and accommodations were all first class."

"It was great! They were very nice at the Institute."

"I had a wonderful time, was treated very well, and would do it again!"

"They gave us too much food at the hotel, but it was fantastic!"

"We met some nice people and had a good time."

"My wife and I had a great time in New Haven. The people with whom I had contact with at the institute were very courteous and professional. Thank you for allowing me to participate in this program."

Thanks- from all of us

Drs. Seegal, Molho and Higgins, Lyndsey, Christine, Julie, Rayna, Sue and Liz would once again like to thank you for taking the time to participate in the Albany and New Haven portions of the study. We look forward to meeting many more of your co-workers, and to the continued success of the project. We simply could not carry out this work without your support.

Want more information?

If you have any questions, or would like more information on the project, please feel free to contact Dr. Rich Seegal at his toll-free phone number 1-866-852-2561.

APPENDIX 3

Abstracts from:

Society of Toxicology,
New Orleans, LA,
March 2005

and

International Neurotoxicology Conference,
Research Triangle Park, NC,
September 2005

SOCIETY OF TOXICOLOGY 2005

Biological Bases for PCB Induced Alterations in Dopamine-Mediated Neurological Function. RF Seegal[1], KL Marek[2], SA Factor[3], RJ McCaffrey[4], RF Haase[4] and AG Kanthasamy[5]. [1]Wadsworth Center, New York State Dept. of Health, Albany, NY; [2]Institute for Neurodegenerative Disorders, New Haven, CT; [3]Albany Medical Center, Albany, NY; [4]University at Albany, Albany, NY and [5]Iowa State University, Ames, IA.

PCBs reduce dopamine (DA) concentrations and the number of tyrosine hydroxylase positive neurons in the substantia nigra of adult rodents and nonhuman primates (NHPs). This loss of function may involve inhibition of monoamine transporters, including the vesicular monoamine transporter, consequent metabolism of cytosolic DA, induction of oxidative stress and apoptosis. Indeed, in a midbrain DA cell line (N27), PCBs induce oxidative stress to a greater extent than MPP+. In order to determine whether these findings induce similar changes in humans we are studying the behavioral and structural consequences of prior long term high level exposure to PCBs in a cohort of former workers. This epidemiological study will determine if prior PCB exposure alters DA mediated behaviors, including motor function, memory and neurological function and the number of DA terminals in the basal ganglia, determined using β-CIT SPECT imaging. This epidemiological study will allow us to begin to determine whether laboratory data demonstrating the neurotoxicity of PCBs can be extrapolated to humans and may provide additional evidence concerning the role of environmental neurotoxicants in the etiology of parkinsonism (*e.g.,* dioxins and furans) on human DA function, including Parkinson's disease. Supported by grants from the US Army Medical Research and Materiel Command, NIEHS and EPA to RFS, and NIH to AGK.

INTERNATIONAL NEUROTOXOCOLOGY CONFERENCE 2005

POLYCHLORINATED BIPHENYLS ALTER DOPAMINE FUNCTION IN OLDER CAPACITOR WORKERS. RF Seegal. *Wadsworth Center, New York State Department of Health and Department of Environmental Health Sciences, University at Albany, Albany, NY, USA*

Polychlorinated biphenyls (PCBs) alter central nervous system (CNS) function, including reductions in central dopamine (DA) function, in laboratory animals. However, their role as a human neurotoxicant is less clear because most environmental exposures to PCBs are via complex mixtures of many additional neurotoxicants. An opportunity exists to minimize this problem by studying the neurological and neuropsychological consequences of occupational exposure to PCBs in an aging population of former capacitor workers. Furthermore, using β-CIT SPECT imaging we can determine PCB-induced changes in basal ganglia dopamine transporter densities and the relationship of these changes with measures of CNS function. Preliminary results suggest that PCB body burdens are statistically associated with reductions in basal ganglia DA densities in women, but not in men. The importance of these findings is strengthened by other recent epidemiological findings of increased Parkinson's disease associated mortality only in highly exposed female capacitor workers. Potential mechanisms for the association between PCB exposure, gender and altered basal ganglia DA function will be discussed. Supported by the Neurotoxin Research Program of the U.S. Army Medical Research and Materiel Command grant # DAMD17-02-0173 to RFS.